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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/383,978	08/26/99	SCHALLER H	BBI-102CP

000959
LAHIVE & COCKFIELD
28 STATE STREET
BOSTON MA 02109

HM12/0524

EXAMINER	
LEE, G	
ART UNIT	**PAPER NUMBER**
1632	7

DATE MAILED: 05/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/383,978	Schaller et al.
Examiner	**Group Art Unit**
Gai (Jennifer) Mi Lee	1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-40 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-40 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4,6

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

This application contains sequence disclosures that are encompassed by the definition s for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Application. Until these requirements are satisfied, the applicant remains in non-compliance with the sequence rules. Please refer to the attached notice to comply. (X)

Priority (X)

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C.119 (e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Specification

The spacing of the lines of the specification is such as to make reading and entry of amendments difficult. New application papers with lines double spaced on good quality paper are required.

The disclosure is objected to because of the following informalities: Pages 4,10, 12-13, 16 of specification, misspelling of IFN α (e.g., a cytokine gene, such as such INFα). Appropriate correction is required.

IFNα.

Claim Objections

Claim 11 is objected to because of the following informalities: A period is needed at the end of the claim. Appropriate correction is required.

Claim 35 is objected to because of the following informalities: Misspelled IFN α in the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 9-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating hepatic disorder or hepatitis infection comprising administering duck hepatitis B virus to the liver for delivery of IFNα, does not reasonably provide enablement for administering any and all hepadnavirus encoding any and all cytokines or any and all heterologous genes in any and all hosts. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 9 is directed to a method of treating a subject with a hepatic disorder comprising: replication defective hepadnavirus particles at a titre level competent to infect hepatocytes of the subject with the hepatic disorder, wherein a region of the preS or S-gene of the hepadnavirus genome has been replaced with a therapeutic gene such that expression of the therapeutic gene is regulated by regulatory sequences of the preS or S-gene; and infecting hepatocytes of the subject

with the hepadnavirus particles such that the therapeutic gene is delivered into the hepatocytes and expressed in the hepatocytes at a level sufficient to treat the hepatic disorder. See claim 1. In further claim embodiments, the hepatic disorder is hepatitis B or C or is selected from the group consisting of hepatocellular carcinoma, cirrhosis, steatosis, hemochromatosis, and inherited liver disorders; wherein the replication defective hepadnavirus particle is the human hepatitis B virus and the heterologous gene is replaced or inserted into the region of the S-gene, such nucleotides encoding at least one amino acid of the S protein are fused in-frame to the 5' end of the heterologous gene or the heterologous gene is inserted after the authentic AUG of the S gene, and the heterologous gene is inserted such that nucleotides encoding at least one amino acid of the S protein are fused in-frame to the 5' end of the heterologous gene. The claim further embodiments, a therapeutic gene of IFNα or selected from the group consisting of IFNγ, IFNβ, IL-18 and TNFα and wherein the hepadnavirus construct is directly administered to the subject or the hepadnavirus construct and a helper construct are cotransfected in vitro and the infectious particle produced from the culture are administered to the subject. See claims 10-22. Claim 23 is directed to a method of treating a subject with a hepatitis infection comprising: a replication defective hepadnavirus particles at a titre level competent to infect hepatocytes of the subject with hepatitis, wherein a region of the preS or S-gene of the hepadnavirus genome has been replaced with a gene encoding a cytokine such that expression of the gene encoding a cytokine is regulated by regulatory sequences of the preS or S-gene; and infecting hepatocytes of the subject with the hepadnavirus such that the gene encoding a cytokine is delivered to the hepatocytes and

expressed in the hepatocytes at a level sufficient to treat the hepatitis. See claim 23. In further claim embodiments, the cytokine is IFNα or cytokines selected from the group consisting of TNFα, IFNβ, IL-18 and IFNγ. The replication defective hepadnavirus particle is the human hepatitis B virus. The heterologous gene is inserted into a region of the S-gene such that nucleotides encoding at least one amino acid of the S protein are fused in-frame to the 5' end of the heterologous gene, the heterologous gene replaces a region of the S-gene, or the heterologous gene is inserted after the authentic AUG of the S-gene, and the heterologous gene is inserted such that nucleotides encoding at least one amino acid of the S protein are fused in-frame to the 5' end of the heterologous gene. The hepadnavirus particle is directly administered to the subject. See claims 24-32.

The claimed invention is directed to effecting gene therapy by way of administering any and all hepadnavirus encoding any and all cytokines or any and all heterologous genes in any and all mammalian hosts and achieving "treatment" of hepatic disorder or hepatitis infection. While, in the Examples, the specification teaches a duck hepatitis B virus constructs comprising a replacement of foreign sequences in the small envelope (S) gene, and maintain genomic size with respect to the wild type could be efficiently produced (pages 17-23). The specification further teaches a stable expression of the foreign gene was observed as long as viable hepatocytes could be kept in culture, with some variation in the intensity of green fluorescence between hepatocytes (page 26). The specification discloses the IFN gene transfer by recombinant DHBV interferes with the establishment of DHBV infection (pages 27-28). The specification further discloses that

no change in DHBV progeny production was seen upon superinfection with rDHBV-GFP, indicating the inhibition was caused by the transduced IFN gene (page 28). The specification also discloses hepadnaviral gene transfer by HBV is species and hepatocyte-specific (page 30).

With respect to enablement of claims directed to gene therapy or treatment, as this is an unpredictable art, a clear correlation to achieving therapeutic expression as broadly claimed must be provided by the specification. With regard to *in vivo* gene expression, Eck & Wilson go on to report that numerous factors complicate *in vivo* gene therapy with respect to predictably achieving levels and duration of gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, *etc.*), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. See page 82, column 1, first paragraph. These factors differ dramatically based on the route of administration of the vector, the protein being produced, and the disease and/or host being treated. As such, the specification fails to provide guidance for any of the above parameters for *in vivo* gene expression nor do they provide a clear correlation to carrying out methods for therapeutic gene transfer protocols as broadly claimed. Instead, the specification teaches only limited transduction of the hepatocytes *in vitro*.

Thus, the cited prior and post-filing art clearly indicates an unpredictable status of the gene therapy art. And, although, specific vectors, promoters, genes, and routes of administration might be or may have been effective for treatment of a specific disease (i.e., hepatic disorder, hepatitis infection) providing a specific therapeutic effect *in vitro*, gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest which results in a therapeutic effect. As the claims are not limited to any specific embodiment of gene therapy nor shown direct correlative effect of rDHBV encoding a gene for IFNα to treating or therapy of hepatic disorder or hepatitis infection, the claimed invention is deemed non-enabled, despite the demonstration of effective transduction of the hepatocytes in vitro with rDHBV-GFP or rDHBV-IFNα of the Examples in the specification.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving treatment of hepatic disorder or hepatitis infection with the claimed invention, in particular where gene therapy is the basis of treatment, the lack of direction or guidance provided by the specification was well as the absence of working examples with regard to achieving treatment of hepatic disorder or hepatitis infection with the rDHBV-IFNα, in particular in the absence of a clinically relevant animal for gene therapy of any and all species-specific hepatic disorders or hepatitis infections, and the breadth of the claims directed to the use any hepadnavirus gene therapy, it would have required undue experimentation of one skilled in the art to make and/or use the claimed invention within the scope of the invention as broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 23, and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9 and 23 are vague and indefinite in its recitation of "level sufficient to treat" because it is unclear what factors are encompassed in the claims to determine what is sufficient and what is not sufficient to treat hepatic disorder or hepatitis. The metes and bounds of the claims cannot be determined.

Claim 39 is vague and indefinite in its recitation of "level suitable for therapeutic use" because it is unclear what factors are encompassed in the claim to determine what is suitable and what is not suitable level for a therapeutic use. The metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 9-16, 21-22, 33, 37-38 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Horwich et al (WO 90/02176).

Horwich et al disclose a replication -defective hepadnaviruses and in particular, two types of defective hepadnavirus genome, and the nucleic acid sequences. Horwich et al disclose the first type ("particle-defective" genomes) are incapable of supplying all hepadnaviral functions required for replication, but are able to produce a pregenome RNA with the appropriate cis-acting signals necessary for inclusion of the RNA in virions ("packaging") and for reverse transcription into DNA. Horwich et al further disclose a second type of defective hepadnavirus genomes ("packaging genome") produced pre-genomic RNA which cannot be packaged and/or reverse-transcribed into a double-strained genomic DNA, and produce messenger RNAs capable of supplying functions required in trans for packaging. Horwich et al also disclose a therapeutic uses of both hepadnavirus packaging genome products and virion particles consisting of packaging particle-defective genomes such as the prevention of hepadnavirus infection or its sequelae and for purposes of gene therapy (abstract). Horwich et al disclose method of expressing heterologous gene in hepatocytes wherein such recombinant viruses may be used for genetic therapy of enzyme production and recombinant hepadnaviruses containing a heterologous gene may be formulated as vaccines for protection against infection by a pathogenic organism or for protection against conditions or disorders caused by the presence of an antigen (page 17). Horwich et al disclose several types of defective hepadnaviruses i.e., duck hepatitis B virus. Horwich et al teach that specific initiation signals are also required for efficient translation of

inserted protein coding sequences. These signals include the ATG initiation codon and adjacent sequences. The initiation codon must be in phase with the reading frame of the protein coding sequences to ensure translation of the entire insert (page 35). Horwich et al further teach that the heterologous gene sequence replaces the genes coding for the surface antigen and viral polymerase protein or can retain pre-S DNA sequences which contain promoters for surface antigen expression (pages 48-49). See entire PCT. Thus, Horwich et al clearly anticipated claims 1-5, 9-16, 21-22, 33, 37-38 and 40 of the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 and 33-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horwich et al (WO 90/02176) taken with Thoma (U.S. Patent #6,020,167).

Horwich et al disclose a replication -defective hepadnaviruses and in particular, two types of defective hepadnavirus genome, and the nucleic acid sequences. Horwich et al disclose the first type ("particle-defective" genomes) are incapable of supplying all hepadnaviral functions required for replication, but are able to produce a pregenome RNA with the appropriate cis-acting signals necessary for inclusion of the RNA in virions ("packaging") and for reverse transcription into DNA. Horwich et al further disclose a second type of defective hepadnavirus genomes ("packaging genome") produced pre-genomic RNA which cannot be packaged and/or reverse-transcribed into a double-strained genomic DNA, and produce messenger RNAs capable of supplying functions required in trans for packaging. Horwich et al also disclose a therapeutic uses of both hepadnavirus packaging genome products and virion particles consisting of packaging particle-defective genomes such as the prevention of hepadnavirus infection or its sequelae and for purposes of gene therapy (abstract). Horwich et al disclose method of expressing heterologous,gene in hepatocytes wherein such recombinant viruses may be used for genetic therapy of enzyme production and recombinant hepadnaviruses containing a heterologous gene may be formulated as vaccines for protection against infection by a pathogenic organism or for protection against conditions or disorders caused by the presence of an antigen (page 17). Horwich et al disclose several types of defective hepadnaviruses i.e., duck hepatitis B virus. Horwich et al teach that specific initiation signals are also required for efficient translation of inserted protein coding sequences. These signals include the ATG initiation codon and adjacent sequences. The initiation codon must be in phase with the reading frame of the protein coding

sequences to ensure translation of the entire insert (page 35). Horwich et al further teach that the heterologous gene sequence replaces the genes coding for the surface antigen and viral polymerase protein or can retain pre-S DNA sequences which contain promoters for surface antigen expression (pages 48-49). See entire PCT. Horwich et al differ from the claims in that the reference fails to disclose insertion of cytokine genes, especially IFNα, into the preS or S-gene region of the replication defective hepadnavirus of the instant invention. However, the secondary reference, Thoma, cure the deficiency. Thoma discloses the therapeutic potential of interferon α wherein it antiviral activity might protect infected cells from infection or reduce viral transcription, translation and replication in HBV-infected cells and that to realize the therapeutic potential, alternative modes of delivery are needed. Thoma discloses that interferon further has immunomodulatory effects by activating T cells, macrophages and NK-cells and by inducing the expression of MHC class I protein (column 2). Note, IFN-α treatment is the current therapy of choice for chronic hepatitis B and C infections and thus, it would be obvious to one of ordinary skill in view of the teachings of Thoma to insert IFN-α genes into a replication defective hepadnaviral vector.

Accordingly, the modification of the vectors of Horwich et al by substituting a gene encoding IFNα as suggested by Thoma in order to obtain a recombinant nucleic acid was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation

of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gai (Jennifer) Mi Lee, whose telephone number is 703-306-5881. The examiner can normally be reached on Monday-Thursday from 8:30 to 5:00 (EST). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on 703-308-2035. The FAX phone numbers for group 1600 are 703-308-4242 and 703-305-3014.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Gai (Jennifer) Lee
Patent Examiner
Art Unit 1600

Jasemine C. Chambers

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